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Evidence for "Stable" Organocopper Intermediates in the Reaction between $Me_2CuLi\cdot LiI$ and Allylic Sulfinyl Mesylates.[1]

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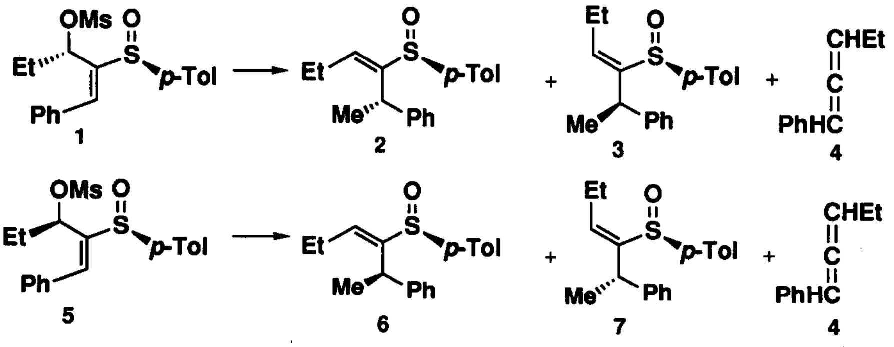
Abstract: The addition of $Me_2CuLi\cdot LiI$ to acyclic allylic sulfinyl mesylates bearing a phenyl functionality in the molecule gives rise to chiral allenes **4** and **11** in variable yields and optical purities, presumably via an unusually stable σ-copper(III) species.

Despite numerous recent studies on the structure of organocopper reagents[2] and on the mechanism of copper (I) mediated conjugate additions to α,β-unsaturated ketones and esters[3] and allylic derivatives,[4] some aspects of these useful reactions[5] remain poorly understood. While the intermediacy of a σ-copper(III) adduct, derived from an initial d,π*-complex, is commonly accepted, experimental data supporting this adduct is scarce, and we are not aware of any report on the direct detection of this transient intermediate.[6] In this paper we describe our preliminary observations on what may be an unusually stable σ-copper(III) species attached to an sp^3 hybridized carbon and its unexpected reactivity upon hydrolysis.

At the initial stage of the development of a new strategy for the asymmetric construction of acyclic chiral centers via conjugate addition of organocuprates to allylic mesylates activated with a chiral sulfoxide group,[7] we found that when the crude solution of unstable mesylate **1** (Scheme 1) was treated with Gilman cuprate $Me_2CuLi\cdot LiI$ in THF (-78°C or -78°→ r.t.) variable but consistently low yields (<25%) of S_N2' products **2** and **3** were obtained. After considerable experimentation we determined, by comparison of our spectral and analytical data with the values in the literature,[6a] that the major product of the reaction was the volatile allene **4**.



Scheme1

We hypothesized that allene **4** was being produced upon aqueous work-up of an unusually stable σ-copper(III) intermediate and therefore we tested different reaction conditions to promote transfer of the ligand on copper before hydrolysis. Indeed, refluxing the crude reaction mixture (ca. 30 min) brought about a substantial increase in yield (80%) without altering the diastereoselectivity of the process (Table 1, entry 2). Alternatively, the use of cyanocuprates, known to undergo a faster reductive elimination,[8] resulted in an increase of selectivity and in virtually complete S_N2' displacement without requiring reflux of the reaction mixture (entries 3 and 4).

Table 1. Reaction between Organocopper Reagents and Allylic Sulfinyl Mesylates 1, 5, 8, 12.

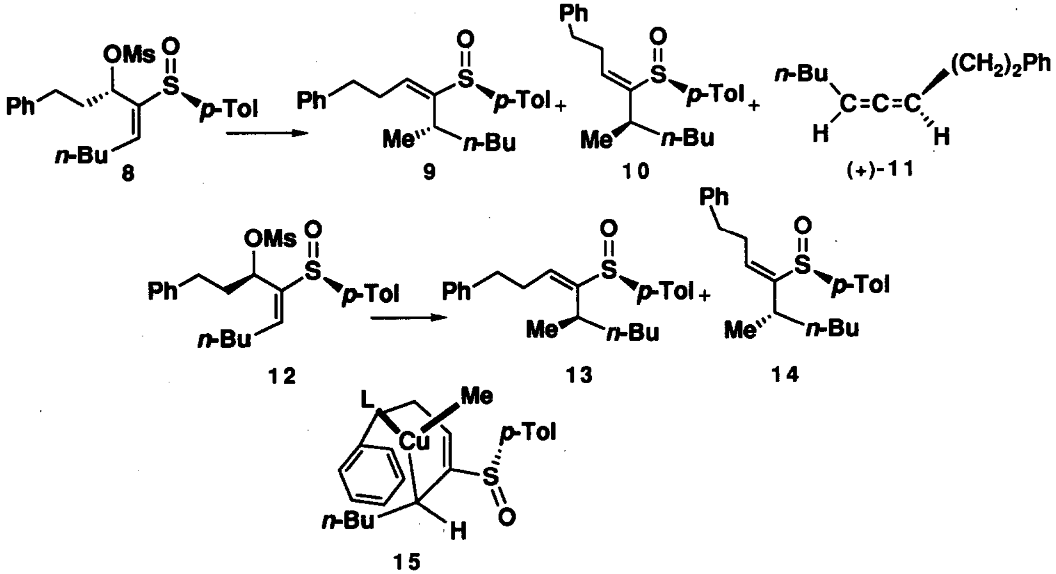
Entry	Substrate	Conditions	S_N2'(ratio)	Allene(α)[a]	S_N2'/Allene ratio[b](yield)[c]	
1	**1**	$Me_2CuLi{\cdot}LiI$(-78°-r.t., 5h)	**2**:**3** (45:55)	**4** (~0°)	27:73	(73%)
2	**1**	$Me_2CuLi{\cdot}LiI$(-78°-Δ)	**2**:**3** (45:55)	Trace	-	(80%)
3[7]	**1**	MeCuCNLi(-78°-r.t.)	**2**:**3** (28:72)	Trace	-	(89%)
4[7]	**1**	MeCuCNMgBr(-78°-r.t.)	**2**:**3** (6:94)	Trace	-	(80%)
5	**5**	$Me_2CuLi{\cdot}LiI$(-78°-0°)	**6**:**7** (6:94)	**4** (-11.0°)	35:65	(76%)
6[7]	**5**	MeCuCNLi(-78°-r.t.)	**6**:**7** (6:94)	Trace	-	(81%)
7[d]	**8**	$Me_2CuLi{\cdot}LiI$(-78°, 20min)	-:-	**11**(+51.1°)	-	
8	**8**	$Me_2CuLi{\cdot}LiI$(-78°, 4h)	**9**:**10** (50:50)	**11**	25:75	(80%)
9	**8**	$Me_2CuLi{\cdot}LiI$(-78°-Δ)	**9**:**10** (85:15)	Trace	-	(85%)
10	**12**	$Me_2CuLi{\cdot}LiI$(-78°, 1h)	**13**:**14** (28:72)	Trace	-	(82%)

[a] In $CHCl_3$. [b] Measured by integration of the ^1H NMR spectrum of the crude reaction mixture. [c] Overall yield of pure products. [d] Under these conditions, ca 50% of allene **11** and ca 50% of starting material **8** were isolated after chromatography.

Diastereomer **5** displayed a similar behavior although the formation of allene **4** appeared to be less favored than for **1** (entries 5 and 6). The very low optical purity found (entries 1 and 5) may be due to allene formation prior to complete quenching of the reagent and racemization by the excess cuprate.[6a] It should be noted that other substrates tested, bearing *n*-Bu and Me substituents instead of Ph, did not produce any allene derivatives even when the reaction mixture was quenched after 15 min at -78°C.[7] However, subsequent experiments performed on pure sulfoxide **8**,[9] surprisingly resulted in variable yields of allene **11**[10] along with starting material or S_N2' products depending upon the reaction time and temperature (entries 7-9). The absolute configuration of **11** was considered to be S by comparison of the sign of its rotation with similar allenes in the literature.[6a] Furthermore, it was observed that the ratio of S_N2' products varied with the reaction conditions, suggesting a faster formation of the minor adduct, perhaps due to a less stabilized Cu(III) intermediate.[11] In contrast, diastereomer **12** yielded only trace amounts of allene **11** (entry 10),thus showing that the steric and/or electronic requirements of this process are very strict.

These results may be tentatively rationalized in terms of irreversible formation[4] of a σ-copper(III) adduct, a simplified depiction of which is shown in structure **15** (Scheme 2) for the case of mesylate **8**. Isomerization of **15** to a π-allyl complex[3,4] seems unlikely considering the clean S_N2' nature of our methodology. When L=Me, reductive elimination is relatively slow, especially in this particular case due to a relatively strong arene-copper stabilizing interaction. Subsequent hydrolysis (saturated NH_4Cl) yields allene **11** by a mechanism that we do not fully understand but believe to be formally *via anti* elimination. To the best of our knowledge, this remarkable transformation is unprecedented in the literature.[12] It is unlikely that this unusual "elimination" takes place on the initial d-π* complex since quenching of these complexes generally leads to recovered starting material;[3f] however, at the time we cannot rule out this possibility. On the other hand, in the case of substrates **1** and **5**, the stabilizing interaction between the aryl ring and copper is probably of different nature due to the benzylic character of the copper(III) intermediate postulated.

This hypothesis is further supported by two facts: 1) Allenes **4** and **11** are obtained in high chemical yields but low enantiomeric purities in all cases upon reaction of the corresponding mesylates (**1**, **5**, **8**, **12**) with MeMgBr or MeLi (THF, 0ºC).[13] 2) Preliminary studies with racemic *tert*-butylsulfinyl analogs show that even MeCuCNLi yields considerable amounts of allenes in some cases. Therefore it appears that the copper mediated case does not proceed *via* nucleophilic displacement on sulfur[14] and that a more electron donating sulfinyl moiety significantly favors production of the allenes presumably due to a more stabilized σ-copper(III) intermediate. Additionally, our observations follow closely those of Crabbé on a postulated allenylcopper(III) species,[6b] except for the final elimination step to yield the allenes.



Scheme 2

The scope of this procedure as a new method to synthesize chiral allenes,[15] including the use of optically pure *tert*-butyl sulfoxides[16] as substrates, as well as the utilization of these mesylates to gain further knowledge on the mechanism of organocopper S_N2' displacements by attempting the detection by NMR and the isolation of these intermediates are currently being addressed in our laboratories.

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10. Data of **11**: transparent liquid. R_f= 0.31 (Hexane). $[\alpha]_D$= +51.1 (c=1.38, CHCl$_3$). IR(CH$_2$Cl$_2$): 3028, 2928, 2857, 1960, 1602, 1495, 1454, 1378, 1260, 872, 747, 738, 734, 722, 712, 700 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0,86-0.91 (m, 3H), 1.30-1.43 (m, 4H), 1.92-1.95 (m, 2H), 2.27-2.43 (m, 2H), 2.71 (t, 2H, J= 7.5 Hz), 5.06-5.12 (m, 2H), 7.16-7.28 (m, 5H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 13.9, 22.2, 28.6, 30.7, 31.4, 35.6, 90.3, 91.5, 125.8, 128.3, 128.6, 142.0, 204.2. MS (EI/70 eV) *m/e*: 200 (M), 157, 144, 129, 91 (100%), 67, 41. High resolution mass spectrum, calculated for $C_{15}H_{20}$: 200.1565. Found: 200.1569. For the preparation of racemic **11**, see: Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5237-5240
11. It should be pointed out that while the stereochemical outcome of the S$_N$2' process remains identical for different batches of CuI, the rate of transfer of the methyl group is remarkably dependent on the procedure of purification employed; in particular, CuI (Fluka, Aldrich) purified from aqueous KI (Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 10) resulted in very fast reductive elimination. Best results were obtained with CuI (Aldrich) washed with refluxing THF in a Soxhlet apparatus. For related puzzling observations see: Alexakis, A.; Mutti, S.; Normant, J. F., *J. Am. Chem. Soc.* **1991**, *113*, 6332-6334.
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13. This reaction is highly dependent on the temperature. For instance, at -20°C the reaction does not take place, while at 0°C, instantaneous formation of the allenes is observed. Allene **11** prepared from **12** and MeMgBr displayed $[\alpha]_D$= -10.3°.
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